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EXAMINER	
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ART UNIT	PAPER NUMBER
1634	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/671,007	RASKIND ET AL.	
	Examiner	Art Unit	
	Diana B. Johannsen	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-6 and 43-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-6 and 43-46* is/are rejected.

7)☒ Claim(s) *4-6* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 29, 2008 has been entered.

2. Claims 1-2, 4-6, and 43-45 have been amended. Claims 1-2, 4-6, and 43-46 remain under consideration.

Election/Restrictions

3. Applicant's election with traverse of the sequence of exon 4 in the reply filed on January 14, 2008 is again acknowledged.

4. With regard to claim 43, nucleic acid sequences other than the elected sequence (i.e., the sequence corresponding to exon 4) noted above are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the replies filed on September 28, 2007 and January 14, 2008.

5. With regard to applicants' comments at pages 13-14 of the Remarks of July 29, 2008, it is noted that instant claim 1 has not been allowed. However, should a generic

claim be allowed at a future date, applicants' request and comments with regard to rejoinder will be given consideration at that time.

Claim Objections

6. Claims 4-6 are objected to because of the following informalities: claim 4 recites a method of "restriction fragment length polymorphism" rather than, e.g., "restriction fragment length polymorphism analysis" (as is recited, e.g., in dependent claim 6). Appropriate correction is required.

Claim Rejections - 35 USC § 112, second paragraph

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1-2, 4-6, and 43-46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-2, 4-6, and 43-46 are indefinite because it is unclear how the recitation of SEQ ID NO: 3 in the claims actually limits the claims. Step (b) of claim recites "identifying a difference between the first nucleic acid sequence from the first human subject exhibiting adult onset cerebellar ataxia and SEQ ID NO: 3, wherein the difference alters the amino acid sequence encoded by the human protein kinase C gamma gene." However, the claims make clear that the recited "first nucleic acid sequence" may be, e.g., just a small portion of the protein kinase C gamma (PKC gamma) gene – for example, dependent claim 4 recites a first nucleic acid sequence that is the exon 4 coding region – thus, the embodiment of claim 4 appears to require a

comparison of a "first nucleic acid sequence" with an approximately 100 nucleotide region contained with SEQ ID NO: 3 (a sequence many thousands of nucleotides long). Similarly, dependent claim 2 references amplifying any "portion of" the human PKC gamma gene. It is unclear how, or even whether, SEQ ID NO: 3 *per se* is actually required with regard to such embodiments; the language of the claims do not make clear how this sequence is actually employed in the practice of the claimed invention, as is necessary to apprise one of skill in the art as to what types of methods would or would not infringe the claimed invention. Accordingly, clarification is required.

Claims 1-2, 4-6, and 43-46 are unclear because it is not clear whether the claims are drawn to a method of "identifying genetic mutations," as set forth in the preamble of claim 1, or to a method in which a single "difference" between two sequences is identified and confirmed as being a "genetic mutation." Accordingly, clarification is required with respect to whether the claims encompass a single mutation or require the identification of multiple mutations.

Claim Rejections - 35 USC § 112, first paragraph

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-2, 4-6, and 43-46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods comprising identifying the H101Y and/or S119P PKC gamma gene mutations in a human subject and "confirming" those mutations as being associated with adult onset cerebellar ataxia in a human

subject, does not reasonably provide enablement for methods comprising identifying and "confirming" any other PKC gamma gene mutations as being associated with adult onset cerebellar ataxia. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (A) the breadth of the claims; (B) the nature of the invention; (C) the state of the prior art; (D) the level of one of ordinary skill; (E) the level of predictability in the art; (F) the amount of direction provided by the inventor; (G) the existence of working examples; and (H) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (*MPEP* 2164.01(a)).

The claims are drawn to a method of "identifying genetic mutations that are associated with adult onset cerebellar ataxia in a human subject" comprising "determining a first nucleic acid sequence" of a human protein kinase C gamma ("PKC gamma") gene from a "first human subject exhibiting adult onset cerebellar ataxia," "identifying a difference between the first nucleic acid sequence" and SEQ ID NO: 3, wherein "the difference alters the amino acid sequence encoded by the human protein kinase C gamma gene," and "confirming that the difference identified between the first nucleic acid sequence and SEQ ID NO: 3 is a genetic mutation associated with adult

onset cerebellar ataxia by co-segregation analysis comprising determining that the identified nucleic acid sequence difference is also present in a plurality of human subjects exhibiting adult onset cerebellar ataxia and is absent in a plurality of human subjects not exhibiting adult onset cerebellar ataxia."

It is unpredictable as to whether one of skill in the art could use applicants' invention in a manner commensurate with the instant claims. Applicants' specification does disclose two particular PKC gamma gene mutations that one of skill in the art would recognize as having been identified and "confirmed" by the method of the invention, and which one of skill in the art would reasonably consider to be "associated with adult cerebellar ataxia." Particularly, the specification discloses a particular exon 4 mutation, the "C to T transition in nucleotide 301 (H101Y)," that was identified by screening the protein kinase C gamma gene in healthy and diseased populations of human subjects, and which is clearly associated with a particular type of ataxia (the "unexplained cerebellar ataxia" discussed in Example 1, which constitutes a type of adult onset cerebellar ataxia)(see Example 1; see also page 6, lines 23-32). Specifically, the specification teaches that this particular mutation was found in 10 members of an affected family "and segregated with ataxia in all ten cases," and not found in any of 192 normal controls (page 25, lines 12-21). It is noted that the specification also teaches that the His 101 residue is in a Cys2 region that is "evolutionarily conserved in all mammals and invertebrates studied and in all Cys2 regions in the PRKCG family" (page 25, lines 19-21). Further, the specification discloses a second exon 4 mutation, a T355C transition encoding S119P, that is

present in an affected woman and her two children, and absent in 96 control samples (see page 26, lines 5-10; 16-17). The specification further teaches that "Serine residue 119 is conserved in all mammalian cys2 regions and most PRKCG family members" (page 26, lines 8-10). Although the specification only exemplifies detection of this mutation in a few ataxic individuals, the specification further establishes that the S119M mutation is encoded by the same exon and located in the same critical domain as the H101Y mutation, and that the mutation is similarly located at a conserved position in that domain; thus, the preponderance of the evidence suggests an association between this mutation and ataxia, such that the claimed invention is enabled with regard to S119M. However, applicants' data with regard to these two particular mutations is insufficient to enable the invention as it is broadly claimed. It is noted that the specification recites a variety of other mutations that have not been "confirmed" as set forth in step (c) of claim 1, such that they do not meet the requirements for being confirmed as "associated with adult onset cerebellar ataxia" as recited in the claims based on the data reported in the specification (see, e.g., Table 3, and Examples 2 and 4 with regard to mutations identified in a single ataxic individual). However, the claims as written apparently encompass methods in which the identification of any of these mutations, or any other missense mutation present anywhere in the PKC gamma gene, in any "plurality" of human subjects with adult onset cerebellar ataxia, and the absence of the same mutation in any plurality of control subjects (e.g., any two control subjects), would result in one concluding that the mutation(s) is(are) "associated with adult onset cerebellar ataxia." One of skill in the art would not reasonably conclude that an

association with adult onset cerebellar ataxia exists based on such limited findings; rather, a skilled artisan would require, e.g., the establishment of an association that is significant based on statistical analysis, or, e.g., another valid basis for concluding that a particular mutation is disease associated, similar to the conclusions noted above with regard to the S119M variant (i.e., the mutation affects a critical domain such that it would reasonably be expected to alter the function of a protein in manner causative of disease symptoms). While the population of mutations "confirmed" by the methods as presently claimed might indeed include some mutations that would eventually be shown to have a genuine association with adult onset cerebellar ataxia, that population would also be expected to include a variety of mutations without such an actual association, and it is unknown as to whether any amount of further experimentation would result in the identification of additional mutations (i.e., mutations in addition to H101Y and S119P) with an actual association with adult onset cerebellar ataxia. Such a quantity and type of experimentation is clearly undue. Lacking guidance from the specification, one of skill in the art may look to the teachings of the prior art for further guidance regarding enablement of a claimed invention. In the instant case, the prior art as exemplified by Chen et al (Am. J. Hum. Genet. 72:839-849 [April 2003]; cited in the IDS of February 15, 2007) appears to report the same data provided in applicants' specification (see the rejection under 35 USC 102(a) set forth below), and does not provide any further evidence contributing to the enablement of the instant claims. The prior art is otherwise silent with regard to mutations in the human PKC gamma gene that are associated with adult onset cerebellar ataxia. Accordingly, while the teachings

of the specification are sufficient to enable methods comprising identifying the H101Y and/or S119P PKC gamma gene mutations in a human subject and "confirming" those mutations as being associated with adult onset cerebellar ataxia in a human subject, it would require undue experimentation to use applicants' invention as it is broadly claimed.

It is noted that applicants' remarks in the reply of July 29, 2008 with regard to the prior rejection for lack of enablement have been considered; however, those arguments are moot in view of the new grounds of rejection presented herein.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

12. Claims 1-2, 4-6, and 43-46 rejected under 35 U.S.C. 102(a) as being anticipated by Chen et al (Am. J. Hum. Genet. 72:839-849 [April 2003]; cited in the IDS of February 15, 2007).

It is noted that the inventive entity of the Chen et al reference differs from that of the instant application. Further, as provisional application 60/414,816 does not disclose all limitations of the invention presently claims (particularly, because SEQ ID NO: 3 is not disclosed in the '816 provisional application), the instant claims are entitled to an effective filing date of September 25, 2003. Thus, the Chen et al reference qualifies as prior under 35 USC 102(a) with respect to the instant claims.

The claims are drawn to a method of "identifying genetic mutations that are associated with adult onset cerebellar ataxia in a human subject" comprising "determining a first nucleic acid sequence" of a human protein kinase C gamma ("PKC gamma") gene from a "first human subject exhibiting adult onset cerebellar ataxia," "identifying a difference between the first nucleic acid sequence" and SEQ ID NO: 3, wherein "the difference alters the amino acid sequence encoded by the human protein kinase C gamma gene," and "confirming that the difference identified between the first nucleic acid sequence and SEQ ID NO: 3 is a genetic mutation associated with adult onset cerebellar ataxia by co-segregation analysis comprising determining that the identified nucleic acid sequence difference is also present in a plurality of human subjects exhibiting adult onset cerebellar ataxia and is absent in a plurality of human subjects not exhibiting adult onset cerebellar ataxia."

It is noted that the claims as written do not actually require the use of, e.g., a molecule consisting of or comprising instant SEQ ID NO: 3, or otherwise clearly require the use of "SEQ ID NO: 3" in its entirety; rather, the claims encompass identifying any difference between the "first nucleic acid sequence" of claim 1 and the sequence recited in SEQ ID NO: 3, such that SEQ ID NO: 3 in its entirety is not in fact required to actually practice the claimed method. For example, dependent claim 43 is drawn to a "first nucleic acid sequence" that "is a coding region of the" PKC gamma gene selected from.....(wherein the elected invention is "exon 4"). Thus, the claim appears to require performing a comparison between the exon 4 sequence that is the "first nucleic acid sequence" and the portion of SEQ ID NO: 3 that allows one to identify whether "the

difference alters the amino acid sequence encoded by" the PKC gamma gene of the subject.

Chen et al disclose methods in which the coding regions of the PKC gamma genes of individuals suffering from adult onset spinocerebellar ataxia (i.e., a form of adult onset cerebellar ataxia as encompassed by the instant claims) were sequenced, resulting in the identification of missense mutations in the gene as compared to the wild-type PKC gamma gene sequence (see entire reference, particularly page 841). Each of the missense mutations identified by Chen et al constitutes a difference with respect to the exon 4 sequence of instant SEQ ID NO: 3, as depicted in Figure 3 of Chen et al (which depicts both the wild-type and variant sequences; the following portions of instant SEQ ID NO: 3 are identical to the "normal" sequences depicted in Figure 3 of Chen et al: 7595-7603 for "A"; 7649-7657 for "B"; 7676-7684 for "C"). Thus, Chen et al teach steps meeting the requirements of (a) and (b) of claim 1 for three mutations that were found in three different ataxic individuals: a missense mutation encoding H101Y, a missense mutation encoding S119P, and a missense mutation encoding G128D (see page 843 and page 845, left column). Further, Chen et al disclose confirming that two these identified missense mutations are associated with adult onset cerebellar ataxia by co-segregation analysis that comprises determining the presence of the missense mutation in multiple subjects also exhibiting the disease and the absence of the missense mutation in multiple subjects not exhibiting the disease; i.e., by steps meeting the requirements of (c) of claim 1 (see page 841 for methodology, page 843 and page 845, left column for results). Particularly, the missense mutation encoding H101Y was

found in 9 family members affected with disease, and not found in 192 normal controls (page 843), and the S119P was found in a total of 3 individuals (an affected woman and her affected son and daughter; see page 845, left column), and not found in any of 192 normal controls. Thus, Chen et al teach methods meeting the requirements of independent claim 1. (It is noted that Chen et al's methods with regard to the G128D mutation do not meet the requirements of the instant claims, as the mutation was found only in a single individual).

With further regard to claim 2, Chen et al disclose amplification of genomic DNA and PCR amplification of each exon followed by sequencing of amplification products, and therefore teach the method of claim 2 (see page 841). Regarding claims 4-6, Chen et al disclose co-segregation analysis by PCR amplification and sequencing for the missense mutation encoding H101Y, and by PCR-RFLP for the other two mutations (see page 841), such that all of the limitations of claims 4-6 are met. With further regard to claims 43-44, it is again noted that Chen et al disclose a first nucleic acid sequence that is a the PKC gamma gene exon 4 coding region (specifically, a PCR amplified exon 4 sequence; see again page 841, and the entire reference). Regarding claims 45-46 it is again noted that each of the mutations taught by Chen et al are missense mutations (see, e.g., page 843 and page 845, left column).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana B. Johannsen whose telephone number is

571/272-0744. The examiner can normally be reached on Monday through Friday, 7:30 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571/272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Diana B. Johannsen/
Primary Examiner, Art Unit 1634

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